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Review

Synaptic Impairment in Alzheimer's Disease: A Dysregulated Symphony

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Alzheimer's disease (AD) is characterized by memory loss, cognitive decline, and devastating neurodegeneration, not only as a result of the extracellular accumulation of beta-amyloid peptide (Aβ) and intracellular accumulation of tau, but also as a consequence of the dysfunction and loss of synapses. Although significant advances have been made in our understanding of the relationship of the pathological role of Aβ and tau in synapse dysfunction, several questions remain as to how Aβ and tau interdependently cause impairments in synaptic function in AD. Overall, more insight into these questions should enable researchers in this field to develop novel therapeutic targets to mitigate or delay the cognitive deficits associated with this devastating disease.

Synapses Disruption As a Key Factor for Alzheimer's Disease

AD is a devastating neurodegenerative disorder that impairs memory and causes cognitive and psychiatric deficits. Currently, AD afflicts over 35 million people throughout the world, including 5.4 million individuals in the USA alone, with a new case developing every 66 sec. AD is the sixth leading cause of death in the USA, killing more people than breast and prostate cancer combined [1,2]. Given that there are no treatments to prevent or reverse AD, in the absence of new breakthroughs, the cumulative costs of care for patients with AD are predicted to bankrupt healthcare systems worldwide.

The urgency of the global AD challenge has led to increased efforts over the past decade to better understand the causes of the disease. Evidence from epidemiological studies shows that synapse loss correlates strongly with the cognitive deficits seen in AD, suggesting a causal role for dwindling synaptic integrity in the etiology of AD. Clinical studies utilizing familial forms of AD, along with animal modeling, have widely documented the importance of Aß pathology in the progression of AD. Notably, studies investigating the molecular relationship between Aß, tau, and synaptic deficits and/or loss, have shed light on how these pathologies could ultimately lead to cognitive decline in patients. The identification of several potential pre- and postsynaptic pathways may contribute to the underlying clinical symptoms of AD. Here, we discuss the current understanding of the mechanisms that link Aß and tau to synaptic and cognitive dysfunction, as well as the findings and conclusions of animal models and clinical studies related to synaptic deficits and/or loss and how therapeutic approaches focusing on the synapse may shed light on a cure for AD.

Trends

AD afflicts over 35 million people throughout the world, including 5.4 million individuals in the USA alone, with a new case developing every 66 sec.

Synaptic loss is the best predictor of the clinical symptoms of AD and the mechanisms by which this deficit occurs is an intense area of investigation.

Aβ oligomers have been classified as types 1 and 2; the latter appears to contribute to synaptotoxicity.

Tau can translocate from axons to the somatodendritic compartment and into spines, where it might interfere with synaptic function.

Significant advances have been made during the past years regarding the actions, interactions, and pathological role of Aβ and tau in synapses, yet many different questions for a better understanding of how Aβ and tau are connected to impair the synaptic function remain.

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New Insights into an Old Friend: Amyloid-Beta Species and the Synaptic Impairment

Aβ is a peptide produced through the sequential cleavage of amyloid precursor protein (APP), with the 40- and 42-amino acid residue peptides being the predominant species. When APP is cleaved by α-secretase, its large amino (N)-terminal ectodomain is secreted into the extracellular medium. The resulting fragment is retained in the membrane and then is either cleaved by β- and γ-secretases to produce soluble Aβ or coalesces under a beta-sheet conformation to form toxic, soluble, low-molecular-weight (LMW; dimers, trimers, and tetramers) and high-molecular-weight (HMW) Aβ oligomers. These may also precipitate to form insoluble fibrils that deposit in senile plaques [3]. For many years, the main idea postulated in the so-called 'amyloid hypothesis' was that amyloid plaques lead to neurodegeneration, cell death, and cognitive decline. However, a growing body of evidences indicates that plaques alone are not responsible for the impairments observed in AD, especially given that synaptic alteration is the best pathologic correlate of cognitive dysfunction in AD. That does not mean that Aβ is not neurotoxic, but recent controversies with clinical trials [4] and numerous studies over the past years have shown us that one swallow does not make summer: that is, Aβ plaques alone do not impair cognition. Increasingly, it appears that Aβ dyshomeostasis is one of the main factors in AD pathogenesis, and we should expand our view towards a multitarget approach to achieve better therapeutic treatments [5–8].

The idea that Aβ oligomers are the main toxins responsible for synapse dysfunction and cognitive deficits in AD has attracted considerable attention to aid our understanding of the mechanisms of the disease [9]. Despite the evidence that low concentrations of Aβ oligomers may enhance synaptic plasticity and cognitive functions in mice [10–12], increased levels of soluble toxic oligomers are found in the cerebrospinal fluid (CSF) and associated with a subset of small synapses near plaques in the brains of patients with AD, but not in those without AD [13–15]. Soluble oligomers may affect normal synaptic functions by inhibiting long-term potentiation (LTP) or facilitating long-term depression of excitatory synapses, consequently contributing to the cognitive dysfunction observed in AD [16]. However, there are still controversies about the specific sizes and types of Aβ that promote synaptic impairment. It is possible that HMW oligomers induce transient memory impairment, while the alterations in synaptic composition and density caused by LMW oligomers lead to more persistent memory impairments due to synaptic loss and reduction in memory consolidation [15,17]. Recently, Yang and collaborators demonstrated that HMW oligomers, which comprise the majority of Aβ species in the AD brain and do not present significant cytotoxic activity, can dissociate into LMW oligomers capable of impairing hippocampal LTP [18]. In another study, Liu and collaborators classified oligomers in mice as type 1 (recognized by the A11 antibody) and type 2 (OC immunoreactive), and observed that type 2 oligomers were less toxic because they were contained inside plaques. A subsequent study revealed that these type 2 oligomers are present in synapses, where they contribute to synaptotoxicity [19]. In this regard, reducing the availability of LMW oligomers could constitute an effective strategy to limit synaptic toxicity. Indeed, a short L-amino acid Aβ-oligomer interacting peptide (AIP) that targets and neutralizes toxic Aβ oligomers not only suppresses their aggregation into proto-fibrillar structures, but also diminishes the loss of synaptic spine density and rescues LTP in cultured hippocampal slices [20]. Moreover, Zahns and colleagues built a significant case for the Aβ*56 oligomers [21]. They demonstrated that these specific oligomers, but not dimers or trimers, were correlated with two pathological soluble tau proteins and inversely correlated with postsynaptic proteins in intact subjects. Also, Aβ*56 oligomers are the only ones that appear to participate in the amyloid cascade before the onset of symptoms [21–23].

Another longstanding debate is whether the Aβ oligomers present at synapses originate from intracellular or extracellular sources, and there is evidence supporting either view. Intracellular

Aβ oligomers have been identified in cholinergic neurons in adult human brain explants, while the number of intermediate and large oligomeric assemblies increase with aging and AD [24]. Brain expression of MAP2 in young Tg2576 mice is reduced at dendritic and postsynaptic sites of Aβ42 monomer and LMW oligomer accumulation [25]. This early intraneuronal pathology was also observed in a transgenic rat model, where a mixture of molecular species with a considerable amount of Aβ had deleterious effects even several months before amyloid plaque deposition [26]. Although many studies demonstrate the importance of intracellular Aβ [18,27,28], there are also data showing that these peptides are secreted from cells. Microdialysis experiments in living mice demonstrated an age-dependent increase of HMW and LMW oligomers in brain interstitial fluid, which constitutes good proof for the existence of extracellular pools of oligomers [29]. Exogenous oligomers accumulate particularly at synaptic spines, and presynaptic sites can also be targeted [30]. Using advanced imaging techniques, Pickett and collaborators recently demonstrated that Aβ oligomers derive from the extracellular plaque halo and accumulate at excitatory synapses more abundantly at postsynaptic than at presynaptic sites, but clearly both sides of the synapse are affected. The authors also showed that there are multiple forms of synaptotoxic oligomers at synapses around plaques [19]. Importantly, γ-secretase is also found in both pre- and postsynaptic compartments, being enriched in the postsynaptic membrane surrounding the synaptic cleft, and this distribution changes according to the stages of synapse maturation [31]. One of the proposed mechanisms for oligomeric synaptotoxicity includes binding of oligomers to postsynaptic receptors [32]. The distance between postsynaptic receptors and the postsynaptic plasma membrane where oligomers could be formed is close, building a strong case for the synaptotoxicity mechanism. The neurotoxic effects of Aβ oligomers are the result of their interaction with different particular cell surface proteins that act as toxin receptors [33]. These oligomers can interact with both ionotropic and metabotropic glutamate receptors, and it has been recently demonstrated that Aβ leads to the ubiquitination of glutamate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) and the recruitment of Nedd4-1, an ubiquitin ligase required for the oligomer-induced reductions in surface AMPARs, dendritic spine density, and synaptic strength [34]. Also, binding of oligomers to one or more specific receptors could facilitate an NMDA-dependent signaling pathway that would lead to the removal of the AMPA receptor subunit GluA3, which is critical for the synaptic deficits [35]. This could be mediated by protein interacting with C-kinase 1 (PICK1) that, in addition to PKCα, is notably necessary for Aβ-mediated synaptic depression [36,37]. The mGluR5 has also been commonly believed to be an oligomer receptor [38,39], especially for its close interaction at the neuronal plasma membrane with the cellular prion protein-containing oligomer receptor complex [32], a mechanism with a central role in the pathogenesis of AD [40]. In addition, other receptors, such as the Sigma-2/PGRMC1 [41,42], the α7-nicotinic receptor [43], Ephrin A4 (EphA4) [44], among others, have also been described as essential for oligomer toxicity (Figure 1).

In summary, our knowledge of the Aβ peptide has increased significantly over the past few years, but many major questions remain, the answers to which could lead to better target therapeutics.

Tau in the Synapse: Mechanism for Synaptic Decline

Tau is a microtubule-associated protein that has a role in stabilizing neuronal microtubules and, hence, in regulating axonal transport [45,46]. However, new evidence has demonstrated that tau also regulates other important process related to the synaptic function and it is also detected in the dendrites, as well as in pre- and postsynaptic components of normal healthy neurons [47–51]. In Figure 2, we illustrate several of the mechanisms by which tau regulates synaptic function in healthy neurons and may be impaired in AD (Figure 2A) [49,50,52]. First, tau regulates axonal mitochondrial transport and may modulate the numbers of presynaptic mitochondria, which impacts synaptic vesicle release. Second, tau is released into the

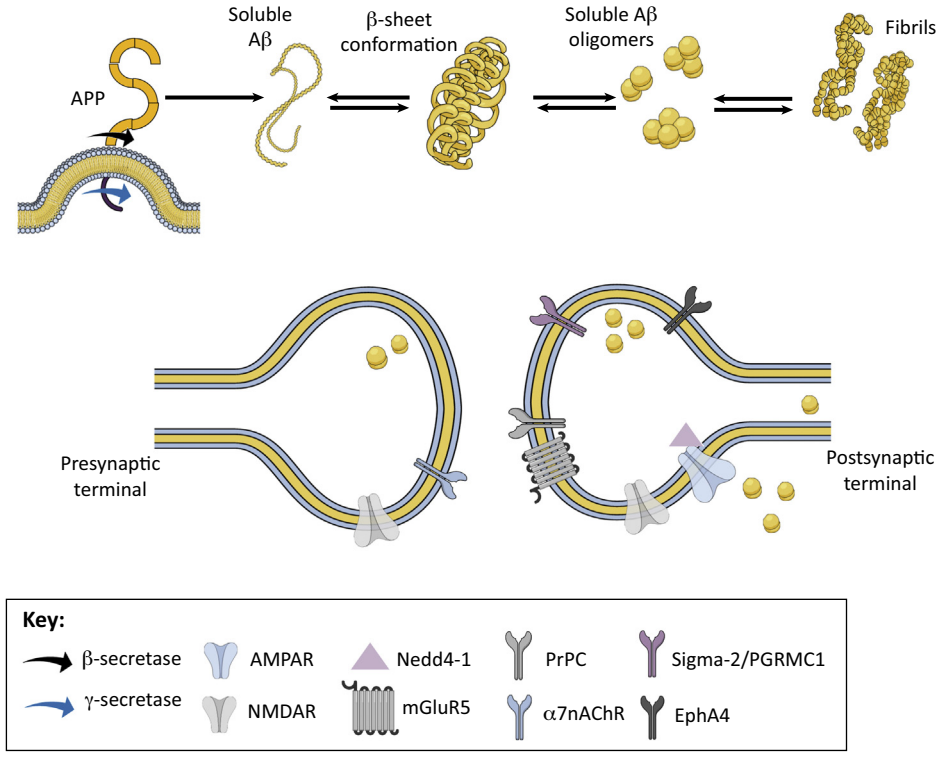

Figure 1. Formation and Mechanisms of Synaptic Toxicity of Beta-Amyloid (Aβ) Oligomers. Amyloid precursor protein (APP) can be cleaved by β- and γ-secretases. Cleavage by β-secretase produces soluble Aβ that adopts a β-sheet conformation that further aggregates to produce soluble and toxic Aβ oligomers. Oligomers can conjugate to form fibrils in amyloid plaques. Once formed, Aβ oligomers may decrease the number of surface glutamate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) via the recruitment of an ubiquitin ligase (Nedd4-1); by binding to different receptors, they can decrease the synaptic strength via an NMDA-dependent pathway. The prion protein-containing oligomer receptor complex (PrPC) may interact with mGluR5, spreading the toxic effect of oligomers. Moreover, oligomers can interact with a variety of receptors on the pre- and postsynaptic membrane of neurons, such as Sigma-2/PGRMC1, the α7-nicotinic receptor, Ephrin A4 (EphA4), among others.

extracellular space, where it can modulate the signaling of synaptic receptors, such as the muscarinic acetylcholine receptor (mAChRs). Third, because tau can directly interact with scaffolding proteins, it can regulate the targeting of glutamatergic receptors to postsynaptic sites in dendritic spines (see below). Finally, tau is a substrate for glycogen synthase kinase-3β (GSK-3β) and p38 mitogen-activated protein kinase (p38MAPK), enzymes found in the post-synaptic compartment that are involved in the regulation of synaptic function, specifically long-term synaptic plasticity. Moreover, recent findings have shown that tau is involved in long-term depression (LTD) in the CA1 of the hippocampus [53,54]. Within the postsynaptic domain, tau enhances the interaction between PICK1 and the GluA2 subunit of AMPARs [55]. This interaction is important for activity-driven AMPAR endocytosis and hippocampal LTD. Overall, these studies suggest that tau exerts a central role controlling the normal function of the synapses.

However, in AD and several neurodegenerative diseases, known as tauopathies, tau under-goes post-translational modifications that affect its affinity towards microtubules [45,46]. This leads to the self-association of tau into neurofibrillary tangles (NFTs), which may alter the axonal transport and other mechanisms described before. The post-translational modifications that tau undergoes in pathological conditions, such as hyperphosphorylation, acetylation, or

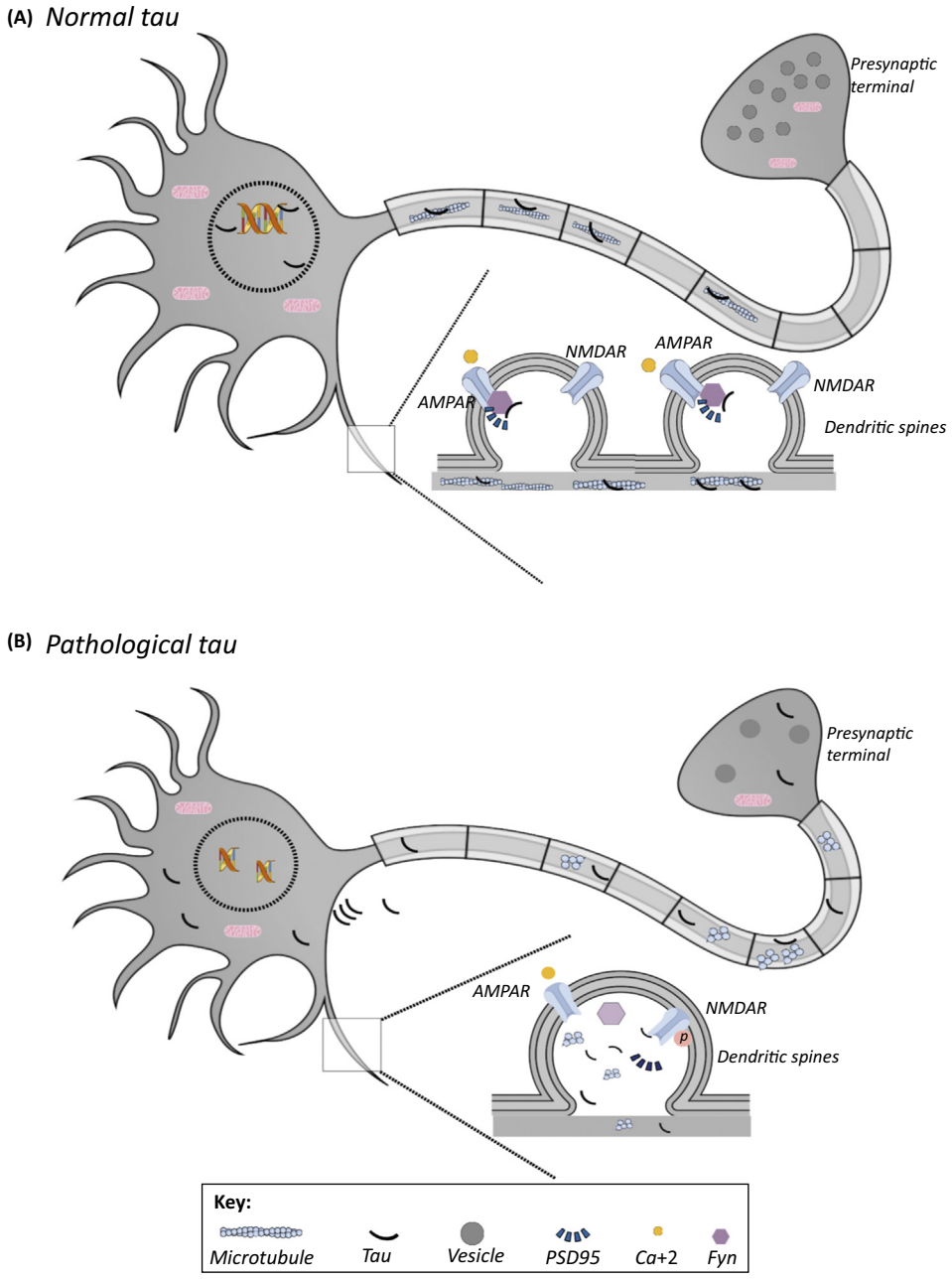

Figure 2. Effect of Tau on Synapses in Healthy Neurons and Tauopathies. (A) In healthy neurons, tau is predominantly found in axons and is responsible for the stabilization of the microtubules. Tau can also be found in dendrites, where it binds to Fyn, which phosphorylates a subunit of the NMDA receptor (NMDAR) and maintains the interaction between the receptor and PSD-95. In addition, there is no change in the number of synapses vesicles in the presynaptic terminals. Likewise, tau is also found inside the nucleus of the neuron, where it maintains DNA integrity. (B) During tauopathies, there is a reduction in the number of dendritic spines. Fyn loses its affinity to PSD-95 and begins interacting only with tau. Meanwhile, glutamate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) are phosphorylated, resulting in their endocytosis. Tau does not enter the nucleus of the neuron, resulting in DNA damage. There is a reduction in the number of mitochondria and also in the number of presynaptic vesicles, which leads to synaptic loss. Such loss is also due to the entrance of tau into dendrites and postsynaptic areas. Tau also aggregates extracellularly, enabling it to be captured by other neurons.

truncation [56–60], can lead to the detachment of tau from microtubules, allowing for its translocation from axons [61] to the somatodendritic compartment and into spines, where it might interfere with synaptic function [45,62]. Post-translationally modified tau molecules tend to self-assemble into paired helical filaments (PHF) forming NFTs. Given that the regional distribution of NFTs in the AD brain correlates well with the severity of cognitive deficits, NFTs were initially assumed to exert toxicity, leading to neurodegeneration. However, cumulating evidence now indicates that soluble tau species, specifically oligomers, rather than NFTs, are toxic tau species [46,47,63–68]. Even if the role of tau oligomers in tauopathies remains a matter of intense debate, due to the incomplete characterization of these molecules, we summarize here recent evidence indicating the mechanisms underlying tau-induced synaptic dysfunction.

In dendrites and the postsynapse, tau interacts with the PSD-95/NMDA receptor (NMDAR) complex. It is postulated that this interaction occurs through direct binding to the tyrosine kinase Fyn, a member of the Src family [54]. Under physiological conditions, the interaction of tau with Fyn targets Fyn to postsynaptic sites, where it can regulate the function of the NMDAR [49,69,70]. In the pathological context, enhanced dendritic tau could serve as a protein scaffold to deliver more Fyn to the postsynaptic sites, which then phosphorylate subunit 2 of the NMDAR (GluN2B) to stabilize a greater proportion of interactions between NMDARs and postsynaptic density protein 95 (PSD-95). This could boost an overactivation of NMDARs during excitatory glutamate neurotransmission, resulting in excitotoxic effects on the neurons affected [50,69,71] (Figure 2B).

Calcium dysregulation is another potential downstream mechanism of pathological tau changes [68,72]. Calcium signaling is thought to be critically important for learning and memory processes, and is known to be altered in human AD brains. Electrophysiological studies in mice overexpressing a human mutant form of tau support a role for elevated calcium levels in AD pathology. In this sense, presynaptic microinjection of recombinant human tau protein resulted in the failure of synaptic transmission, showing that an increase in neurotransmitter release is dependent on calcium released from intracellular stores, accompanied by a reduction in evoked neurotransmitter release [72]. Relatedly, calpains, a family of calcium-dependent cysteine proteases, have been implicated in tauopathy development and neurodegeneration in AD. Moreover, it has previously been demonstrated that calpain-active cdk5 and ERK1/2 kinases can phosphorylate tau and induce innumerable downstream tau-dependent and independent pathogenic effects, including impairments of synaptic plasticity and cognition [73]. In addition, a mechanism by which intracellular accumulation of human wild-type full-length tau impairs synapse and memory functions was proposed. hTau accumulation was found to activate the calcium-dependent protein phosphatase calcineurin (CaN), which then dephosphorylated and/or inactivated nuclear calcium-dependent protein kinase IV (CaMKIV)/cAMP response element binding protein (CREB) signaling, eventually resulting in synaptic and memory impairments [74].

Another proposed mechanism implicated abnormal acetylation of K274 and K281 on tau, a post-translational modification identified in AD brains. This acetylation promotes memory loss and disrupts synaptic plasticity by reducing postsynaptic Kidney/BRAin (KIBRA) protein, a memory-associated protein. Transgenic mice expressing human tau with lysine-to-glutamine mutations to mimic K274 and K281 acetylation (tauKQ) exhibit AD-related memory deficits and impair hippocampal LTP. TauKQ reduces synaptic KIBRA levels and disrupts activity-induced remodeling of postsynaptic actin and AMPAR insertion. Enhanced tau acetylation linked to loss of KIBRA has also been reported in patients with AD and dementia [75].

Tau is also a substrate of multiple caspases, which cleave it and promote its pathologic aggregation [76]. In this regard, it has been recently shown that caspase-2 cleaves tau at Asp314, forming tau314, which reversibly impairs memory function [60]. Also, the intracellular caspase-3 level regulates tau phosphorylation and such an effect is mediated by the GSK3β kinase pathway via caspase-3-dependent cleavage and activation of protein Akt [77]. Likewise, caspase-6 activity is already detectable both in pretangles and preclinically in the entorhinal cortex of some older individuals, indicating that caspase-6 activation is an early event in AD. It has been demonstrated that the levels of caspase-6 in the entorhinal cortex and CA1 correlated negatively with cognitive performances that are initially affected in AD [78]. Caspase-6 causes axonal degeneration once it cleaves cytoskeletal proteins crucial to neuronal integrity and function, such as alpha-tubulin, Tau and postsynaptic density proteins regulating the actin cytoskeleton of the dendritic spines in synapses [79,80].

Finally, pathological changes in tau disrupt microtubule-based cellular transport, thus preventing the trafficking of essential cargo, such as mitochondria and receptors to synapses. Impairment of mitochondrial transport to pre- and postsynaptic terminals is thought to cause synapse loss and eventual die-back of axons due to diminished mitochondria-dependent ATP production and calcium buffering. Moreover, in support of this idea, it has been demonstrated that abnormally phosphorylated tau impairs the trafficking of glutamate receptor subunits GluA1, GluA2/3, and NR1 to the postsynaptic density [81,82].

In conclusion, considerable progress has been made in recent years in our understanding of the roles of tau in physiology and disease. Even though the mechanisms underlying tau-mediated neurotoxicity remain to be fully elucidated, the knowledge accumulated thus far has led to the proposal of multiple therapeutic approaches that target tau function or dysfunction [83,84].

Aβ and Tau: Fellow Travelers towards the Development of Synaptic and Cognitive Impairments

In previous sections of this review, we described multiple mechanisms by which Aβ and tau can impair synaptic function and lead to severe cognitive deficits. Yet, one of the major fundamental questions in the AD field that remains is related to the molecular relationship between Aβ and tau, and how these two players affect the integrity of synaptic function and lead to manifestation of profound cognitive deficits. Accumulating evidence has shown a variety of cell-dependent and -independent pathways by which Aβ can trigger tau pathology [85–87]. For example, studies in 3xTg-AD mice highlight the importance of intraneuronal soluble Aβ as the initial mediator of tau pathology [85]. Other studies showed that Aβ induces tau pathology by altering the levels of the C terminus of heat shock protein 79-interacting protein (CHIP), a known tau ubiquitin ligase responsible for facilitating degradation of hyperphosphorylated tau and caspase-3-cleaved tau [85]. In addition, extracellular Aβ is also involved in the development of tau pathology. Studies using induced neuronal-derived pluripotent stem cells (iPSCs) have shown that extracellularly generated Aβ increased tau levels in fAD neurons [88,89]. Interestingly, it was also demonstrated that extracellular Aβ has an important role in tau pathology mediated by inflammation [90]. Specifically, it was found that interleukin-1β (IL-1β) represents a key mechanism by which Aβ drives the development of tau pathology [90]. Overall, these findings highlight the complexity of Aβ and tau relationships, and support the notion that multiple Aβ-related mechanisms might be responsible for inducing tau pathology in different settings.

At the synaptic level, it has been shown that Aβ promotes tau phosphorylation and its misplaced localization in dendritic projections, and that overexpression of both toxic proteins, Aβ and tau, accelerates synaptic and cognitive impairments [91–94]. Given that Aβ and tau

coexist and interact directly between themselves within the synaptic compartment [47,91,93], both proteins may have a synergic role in affecting normal synaptic functions. Several mechanisms have been proposed to explain how these two pathological proteins interact in the synapses and how Aβ induces tau pathology. A series of *in vitro* studies by Mandelkows's group has provided compelling evidence that Aβ-induced elevation of intracellular calcium levels is a key upstream event for the formation of tau pathology and its misplacement into the dendritic compartment. The elevation of calcium levels initiates the abnormal activation of several kinases, including microtubule affinity-regulating kinase and cyclin-dependent kinase 5, which phosphorylate and misplace tau into the dendritic area, leading to microtubule destabilization, mitochondrial trafficking impairment, loss of mature spines, and diminished synaptic activity [91,95]. Supporting these findings, a recent study from Polleux's lab also revealed that increases in intracellular calcium triggered by Aβ activate AMP-activated kinase (AMPK) induce tau phosphorylation at Serine 262 (S262). Further analyses demonstrated that this event is key to manifestation of the synaptotoxic effects of Aβ [96]. A second putative mechanism suggests that Aβ induces tau pathology by direct interaction with the latter in a prion-like manner [66,87]. *In vitro*, Aβ oligomers can induce tau aggregation and the formation of β-sheet-rich neurotoxic tau oligomers [87]. Indeed, several studies in animal models also suggest that Aβ can also seed tau oligomerization *in vivo* [87]. Therefore, it is plausible that Aβ oligomers within synapses serve as a direct template for misfolding tau and facilitate the formation of tau oligomerization. Recent studies in AD brains have shown the presence of oligomeric forms of tau in synapses, and large (over fourfold) elevations in the concentration of tau in AD samples compared with healthy control samples [47,64,97]. These findings lead to an important question regarding the identification of the pathological role of tau oligomers in AD. Most importantly, several recent studies have shown that tau oligomers are toxic molecules leading to synaptic and mitochondrial dysfunction [97–99]. Furthermore, a reduction of tau oligomers using an immunotherapy approach mitigates the synaptic and cognitive impairments in an APP transgenic mouse [100]. Such findings provide mechanistic insight into the pathological role of interaction between tau oligomers and Aβ in synaptic and cognitive functions.

One of the most convincing demonstrations that synaptic dysfunction depends on the actions of both Aβ and tau is that removing endogenous tau prevents Aβ-associated cognitive deficits [66,86,87,101]. Further studies suggest that tau targets the tyrosine kinase Fyn, a member of the Src family, in the postsynaptic density and induces aberrant glutamatergic synaptic transmission via overactivation of NMDARs [69,92,102,103]. Moreover, Fyn inhibition rescues synaptic and cognitive deficits in a mouse model of AD [104]. However, the scenario is not that simple because several recent studies link Aβ to tau pathology via Fyn kinase. These studies proposed that Aβ could modulate Fyn kinase through the cellular form of the prion protein (PrP^C), resulting in increased tau phosphorylation [32,105]. However, because the molecules that link PrP to Fyn remain unknown, more detailed analyses of the cooperative role of Aβ, PrP and Fyn are necessary. In summary, these findings highlight the central role of Fyn as an important mediator of the detrimental effects of Aβ and tau in synapses.

Here, we have highlighted several of the major putative mechanisms by which Aβ and tau interact and impair the synaptic function (such as intracellular calcium, seeding, and Fyn kinase). However, more progress is necessary to translate these important findings into potential therapeutic strategies to mitigate the synaptic and cognitive symptoms associated with this disorder.

Concluding Remarks

In summary, significant advances in our understanding of how tau impacts synaptic function and is related to the pathological role of Aβ in synapses have been made over recent years. Yet, many questions remain that need to be addressed if we are to better understand how these

Outstanding Questions

How do the pathological isoforms of tau travel to the synaptic compartment?

What makes tau stick within the dendrite and by which pathways can tau affect postsynaptic site functions?

Is prevention of Aβ binding to its receptor sufficient to preserve synapse integrity?

What species of Aβ and tau should be targeted for therapeutic approaches?

Do current animal models reveal the full reality of how Aβ and tau interact and cause synaptic deficits or do different mechanisms occur in humans?

All of the currently available models are based on the rarer, autosomal dominant form of the disease, whereas most AD cases are sporadic. Is it not time for the field to also start focusing on understanding synaptic loss in sporadic AD?

fellow travelers (Aβ and tau) are connected to impair synaptic function. For example, due to the diversity and complexity of Aβ aggregates, it is crucial to investigate the pathological role of these different Aβ assemblies in synapses, and to identify the molecular pathways through which these molecules promote tau pathology and synaptic impairments. Moreover, further studies are needed to identify which pathological tau isoforms triggered by Aβ (including phosphorylation, oligomerizarion, etc.) are misdirected to the synaptic compartment and lead to the synaptic deficits. This is important because a new study has revealed that the site-specific phosphorylation of tau p38γ inhibits Aβ toxicity [106].

Furthermore, a key question in the AD field is to identify the mechanisms whereby pathological isoforms of tau travel to the synaptic compartment (see Outstanding Questions). Overall, more insight into these questions would constitute a major enhancement of our present understanding of the pathological mechanisms by which Aβ and tau affect synaptic functions, and hopefully contribute to the development of novel therapeutic targets to mitigate or delay the cognitive deficits associated with this insidious disease.

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